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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/770,943	RAZ ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8-17-06 and 12-30-06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-36 and 38-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36 and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Five Pgs attached to office action

RESPONSE TO AMENDMENT

The response filed 12-4-06 and amendment filed 5-8-18-06 have been entered into the record. Claims 32-36 and 38-43 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

The rejection of claim 40 under 35 U.S.C. 102(b) as being clearly anticipated by Draper et al (US Patent No. 5,514,577 issued May 7, 1996) for reasons made of record in the Office Action mailed 11-14-05 is withdrawn in view of the amendment to the claims.

The rejection of claims 32, 33 and 35 under 35 U.S.C. 103(a) as being unpatentable over Bennett et al (WO 91/16901, published November 14, 1991) in view of Barsoum et al (WO 94/04686, published March 3, 1994) is withdrawn in view of the amendment to the claims.

The rejection of claims 40 and 41 under 35 U.S.C. 103(a) as being unpatentable aver Draper et al (US Patent No. 5,514,577 issued May 7, 1996) in view of Barsoum et al (WO 94/04686, published March 3, 1994) is withdrawn in view of the amendment to the claims.

The rejection of claims 42 and 43 under 35 U.S.C. 103(a) as being unpatentable over Draper et al (US Patent No. 5,514,577 issued May 7, 1996) and Barsoum et al (WO 94/04686, published March 3, 1994) as applied to claims 40 and 41 above, and further in view of Bennett et al (WO 91/16901, published November 14, 1991) is withdrawn in view of the amendments to the claims.

Rejections Maintained

The rejection of claim 36 under 35 U.S.C. 103(a) as being unpatentable over Bennett et al (WO 91/16901, published November 14, 1991) in view of Barsoum et al (WO 94/04686, published March 3, 1994) is maintained for reasons made of record.

Applicants' arguments have been considered but are not persuasive. Applicants argue that there is no explicit motivation to conjugate the peptide since the prior art did not perceive any difficulty in the antisense nucleic acid per se. This is not persuasive, the use of cargo peptides to facilitate delivery was a well established technique in administering antisense therapy because it would facilitate and enhance delivery *in vitro* and *in vivo* as taught by the prior art. Further, *In re* Fine, 837 F.2d 1071, 1075, 5U.S.P.Q.2d 1959 (Fed. Cir. 1988) states that under section 103 a *prima facie* case of obviousness can be established by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art can lead the individual to combine the references. See also *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Applicants argue that the amendments to the independent claim 32 would obviate this issue. This is not persuasive, claim 36 is an independent claim and therefore not affected by the amendment to claim 32.

The rejection is maintained.

New Rejections Based on Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-35, 38, 39 and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to pharmaceutical compositions comprising a nucleic acid sequence conjugated to an autoantigen or autoantibody. The specification teaches that the compounds of the invention are useful in modulating the imunostimulatory activity of Immunostimulatory oligodeoxynucleotide (ISS-ODN) administered as adjuvants (paragraph bridging pages 2-3 of specification) or reduce host inflammation generated in response to infection by and ISS-ODN containing bacteria or virus. The specification teaches that the immune inhibitory oligodeoxynucleotides (IIS-ODN) autoantigen conjugatges are useful in boosting host Th2 type immune response to the autoantigen (**suppressing** the Th1 responses by the autoantigen itself) and the ISS-ODN autoantibody conjugates are useful in inducing passive immunity in a host suffering from and autoimmune condition. The claims are drawn to pharmaceutical compositions and therefore the compositions must provide for treatment. The teachings of the specification are limited to the passages at pages 18-19.

The alleged switch from a Th1 repsonse to a Th2 response by the IIS-ODN antoantigen conjugate is not enabled to treat or prevent any autoimmune disease or specific diseases contemplated in the specification. The specification teaches that the

inhibitory ODN have the ability to switch the balance of the immune response to immunestimulatory ISS-ODN from a Th1 to a Th2 cytokine profile in vitro. The ability to switch an antigen driven response when the antigen is conjugated to the inhibitory ODN has not been demonstrated. The art recognizes that genetic differences may contribute to control of the TH1/Th2 response (see Conboy et al cited in specification). In contrast to a de novo response, treatment of autoimmune disorders occurs in the face of an on-going and established immune response. The administration of autoantigen conjugate in patients with autoimmunity would be expected to provide for stimulation of the already present and primed Th1 autoimmune response. The Th1 response is antigen driven and there is no evidence of record that ISS-ODN contribute to the on-going autoimmune response and no evidence that the inhibitory autoantigen/autoantibody conjugate has any affect on the ongoing autoimmune response (i.e. ability to inhibit autoantigen-driven response *in vitro* or *in vivo*). The ability to madulate a naïve cell population is quite different then modulating an existing immune response. The failures of modulating existing autoimmune response using atuoantigens are noted in the literature. The art with respect to generation of immunosuppressive responses by antigen was and is still highly unpredictable. It is well known in the art that antigen delivers both immunogenic and tolerogenic signals to lymphocytes, the outcome of which is a complex interaction of many signals. The art teaches that still in 2001, that obtaining the desired response with stimulation of antigen receptors with antigen, is unpredictable because many of these signals have both tolerogenic and immunogenic roles (see Goodnow et al, The Lancet, 357:2115-2121, June 30, 2001; see abstract in particular). Immunological Tolerization is a suppression of a specific immune response and encompasses "active suppression", clonal anergy and clonal deletion see Herbert et al (The Dictionary of Immunology, Academic Press, 1995, page 93. All three mechanisms of tolerance induction, active suppression, clonal anergy and clonal deletion, results in suppression of disease, decreased innmuoproliferative responses and decreased inflammatory responses at the sites of

autoimmune disease. The induced mechanism depends on the antigen dosage and the frequency of administration (Sensei et al, Transplantation Proceedings, 30:545-549, 1998; see abstract). The method and means to generate a tolerogenic as opposed to an immunogenic state, was unpredictable at the time this application was filed and is still unpredictable. Harats et al (WO 02/53092, published July 11, 2002) review recent work and teach "As the above mentioned disclosures clearly demonstrate, the parameters for induction of oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even in vitro results, and must result from extensive empirical experimentation. Indeed, many studies have demonstrated the complexities inherent in manipulating the "balance between reacting and nonreacting" in the immune system. Zivny et al (Clin Immunol, 2001;101:150-68) clear state that "In general, the response to one (tolerance inducing) antigen could not necessarily predict the response to another." Likewise, Hannihen et al (Diabetes 2001; 50:771-75) observed that oral, nasal and respiratory administration of antigens caused appearance of disease symptoms (diabetes), rather than inducing tolerance. Similar inconsistencies in mucosal tolerance have been reported by Fujihasi et al (Acta Odontol Scand 2001;59:301-308), Jiang HR et al (Br J Ophtalmol 2001;85:739-44)." The art at this time Couzin (Science 296(5576:456) teaches that although animal studies have shown promising findings, in humans the work remains highly experimental and a handful of trials have screeched to a halt due to deadly adverse side effects. Unlike the sledgehammer approach of chemical immune suppression, immune tolerance is more akin to a massage (paragraph bridging pages 1-2). Further, the complexity of human studies and the lack of correspondence of the animal models with efficacy in human disease is demonstrated by Marketletter, 13 September 1999, which reported that patients receiving oral Myloral™ (i.e. product containing myelin basic protein) faired no better than placebo and Colloral™ (i.e. product containing collagen) did not produce statistically significant results in humans and a large placebo effect was observed over that of preliminary studies. As such, the promising

animal studies have not panned out for these two drugs in humans. There is no evidence of record that the conjugate inhibits, rather than exacerbating the ongoing established autoimmune response. Even if one could switch to a Th2 response, the autoimmune disease still exists and moreover, the response is merely shifted to produce different isotypes of antibodies that could also be pathogenic. IgE antibodies are certainly pathogenic and involved in atopic responses. The switched antibodies would have the same pathogenic characteristic as the original autoantibodies. The ability to modulate an ongoing autoimmune response to provide for switch to tolerance, suppression of Th1, switch to Th2 cytokine profile or other treatment of autoimmune diseases using autoantigens is highly controversial in the art and the art is replete with teachings that is unsuccessful and unpredictable. With respect to the claimed autoantibody conjugates, it is noted that applicants indicate that such conjugates provide for passive immunity. Passive immunity to what ? Many of the autoantibodies in autoimmune diseases are pathogenic. The antibodies referenced in the specification are pathogenic autoantibodies and contribute in some form to the disease process (i.e. immune conjugate deposition or inflammation; see page 18 bottom paragraph). The concept of the specification is the use of IIS-ODN to switch the autoimmune response from Th1 to Th2. This concept is active immunity. How does the autoantibody conjugate provide for passive immunity and how does passive immunity with the contemplated pathogenic autoantibodies provide for treatment of autoimmune disease. Therefore, it is completely unclear how administering conjugates of pathogenic autoantibodies provide for a switch of the immune response to Th2 cytokine profile (IgE and IgG1 or passive immune treatment of an autoimmune disease.

A review of the art shows that little is known about the induction of a Th2 response for the treatment of autoimmune disease. A review of the specification discloses that the method of the instant claims presumably treats Th1 autoimmune disease by administering an autoantigen or autoantibody conjugated to an ISS-ODN to skew the immune response towards Th2, from the Th1. This method is, again presumably, based on

the theory that there exists a Thl/Th2 balance wherein increasing the Th1 or Th2 response decreases the other. First note that many investigators consider the Thl/Th2 paradigm an overly simplistic way to view highly complex systems. See for example Louzoun et al. (Journal of Autoimmunity, 17:311-321, 2001) and that therapeutic manipulation of the Th1-Th2 balance is inherently dangerous and unpredictable (Brunet et al and Wohlleban et al (Trends in Immunology 23(3):127-128, 2002). Genain et al (Science, 274:2054-2056, 20 December 1996) teach that immune deviation and shift of a cytokine production from a Th1 pattern to a Th2 pattern increased titers of autoantibodies, increase pathogenic autoantibodies and exacerbate autoimmune disease (see abstract). As such, swith to the Th2 type cytokine response is not necessarily correlated with autoimmune disease therapy. Further, the art teaches that autoimmune Th1 responses can develop and continue even in the presence and high frequencies of Th2 cells (Hofstetter et al, Journal of Immunology 169:117-125, 2002). Therefore, it is clear that immune deviation does not predict a therapeutic effect and the Th2 autoantibodies can be pathogenic and exacerbate existing disease. Further, the generation of an autoimmune Th1 response in the presence of an existing Th2 repertoire indicates that the in vivo situation is highly complicated and not as simple as either a Th1 - autoimmune disease versus Th2 - no autoimmune disease.

The specification fails to teach even one conjugate that is successful in generating modulated or switched cytokine response in an antigen-driven *in vitro* model relevant and correlative/predictive of treatment of autoimmune disease *in vivo*. The ability to switch the ability of an IIS-ODN to modulate the cytokine profile of naïve cells stimulated with ISS-ODN *in vitro* is not reflective of the antigen driven response *in vivo* and autoimmune response in particular where there is a pre-existing and ongoing Th1 driven response. The art teaches that a Th1-Th2 cytokine switch or presence is not correlative of a therapeutic response. In view of the controversy in the art regarding the usefulness of autoantigens as therapeutic agents in the treatment of autoimmune diseases, the lack of teaching of

how to use the concept of Th1 to Th2 switch to treat autoimmune disease in general and autoantibodies to treat autoimmune disease by providing "passive immunity" the specification is not enabled for pharmaceutical compositions comprising such.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 40, 42 and 43 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Scholar et al (U.S. Patent No. 5,552,390 filed December 9, 1993).

The claims are drawn to a nucleic acid comprising a hexameric sequence of a particular structure in a pharmaceutically acceptable carrier, wherein the nucleic acid is 6 to 45 nucleotides in length or the hexameric structure is AGGGCT (see claim 40) wherein the nucleic acid comprises one or more phosphorothioate linkages.

Scholar et al teach SEQ ID NO:14 DNA, d(P-thio) (*CAGGGCT*CTCATGGTGGC) see attached file STN registry RN 182332-60-0. Scholar et al teach a pharmaceutical preparation of the inhibitors for treatment of metastatic breast cancer (column 3, line 66 - column 4, line 30) and pharmaceutical compositions in a physiologically acceptable carrier suitable for administration by intravenous injection, intravenous drip or oral form (capsule or tablet). Modifications of the oligonucleotides are taught at column 3, lines 32-47).

Scholar et al teach that HUPA70 (SEQ ID NO:14) inhibited tumor invasion (see Table 6, column 10, Example 3). As such, Scholar anticipates the instantly claimed pharmaceutical compositions.

Claims 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scholar et al (U.S. Patent No. 5,552,390 filed December 9, 1993) in view of Barsoum et al (WO 94/04686, published March 3, 1994).

The claims are drawn to a nucleic acid comprising a hexameric sequence of a particular structure in a pharmaceutically acceptable carrier, wherein the nucleic acid is 6 to 45 nucleotides in length or the hexameric structure is AGGGCT (see claim 40) wherein the nucleic acid is conjugated to a peptide.

Scholar et al teach SEQ ID NO:14 DNA, d(P-thio) (*CAGGGCT*CTCATGGTGGC) see attached file STN registry RN 182332-60-0. Scholar et al teach a pharmaceutical preparation of the inhibitors for treatment of metastatic breast cancer (column 3, line 66 - column 4, line 30) and pharmaceutical compositions in a physiologically acceptable carrier suitable for administration by intravenous injection, intravenous drip or oral form (capsule or tablet). Modifications of the oligonucleotides are taught at column 3, lines 32-47). Scholar et al teach that HUPA70 (SEQ ID NO:14) inhibited tumor invasion (see Table 6, column 10, Example 3). Scholar teach that after administration the oligonucleotides enter the cells, hybridize to mRNA and inhibit the ability of the mRNA to serve as a template for the synthesis of encoded products (column 4, lines 22-30). Scholar et al differ by not attaching a protein to the antisense nucleic acid.

Barsoum et al teach the delivery of cargo molecules, such as nucleic acids to the cytoplasm and nuclei of cells in vitro and in vivo by the use of a transport polypeptides that comprise one or more portions of HIV tat protein which are covalently attached to cargo molecules (see abstract and pages 5-7)

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to conjugate nucleic acid of Scholar et al to the transport peptide(s) of Barsoum et al because Barsoum et al teach that the cargo peptides facilitate and enhance entry of nucleic acids into the cytoplasm and nucleic of cells *in vitro* and *in vivo*.

Status of Claims

All claims stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Jeffrey Siew can be reached on 571-272-0787.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Pat A. Duffy

Patricia A. Duffy

Primary Examiner

Art Unit 1645